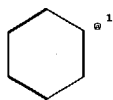


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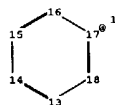
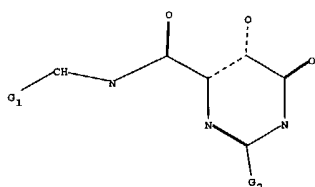


Hy 2

Hy 3

Hy 4

Hy 5

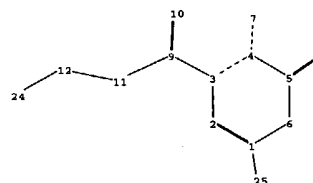


19 2

27 3

28 4

29 5



ain nodes :  
7 8 9 10 11 12 19 24 25 27 28 29

ng nodes :  
1 2 3 4 5 6 13 14 15 16 17 18

ain bonds :  
1-25 3-9 4-7 5-8 9-10 9-11 11-12 12-24

ng bonds :  
1-2 1-6 2-3 3-4 4-5 5-6 13-14 13-18 14-15 15-16 16-17 17-18

act/norm bonds :  
1-2 1-6 1-25 2-3 3-4 4-5 4-7 5-6 5-8 9-10 9-11 11-12 12-24

act bonds :  
3-9

ormalized bonds :  
13-14 13-18 14-15 15-16 16-17 17-18

olated ring systems :  
containing 1 :

:[\*1],[\*2]

:[\*1],[\*2],[\*3],[\*4],[\*5]

atch level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS  
11:CLASS 12:CLASS 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 24:CLASS  
25:Atom 27:Atom 28:Atom 29:Atom

neric attributes :

19:  
Saturation : Unsaturated  
Number of Carbon Atoms : less than 7  
Number of Hetero Atoms : less than 2  
Type of Ring System : Monocyclic  
27:  
Saturation : Unsaturated

Number of Carbon Atoms : less than 7  
Number of Hetero Atoms : less than 2  
Type of Ring System : Monocyclic  
28:  
Saturation : Unsaturated  
Number of Carbon Atoms : less than 7  
Number of Hetero Atoms : less than 2  
Type of Ring System : Monocyclic  
29:  
Saturation : Unsaturated  
Number of Hetero Atoms : 2 or more  
Type of Ring System : Polycyclic

ement Count :

Node 19: Limited

C,C5  
N,N1  
O,O0  
S,S0

Node 27: Limited

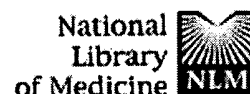
C,C4  
N,N1  
O,O0  
S,S0

Node 28: Limited

C,C4  
O,O1  
N,N0  
S,S0

Node 29: Limited

N,N3  
C,C6  
O,O0  
S,S0



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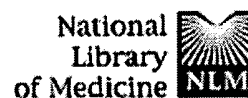
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ELSEVIER SCIENCE  
FULL-TEXT ARTICLE

## Human immunodeficiency virus and host cell lipids. Interesting pathways in research for a new HIV therapy.

Raulin J.

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raulinj@hotmail.com

It has been reported in the literature that biological membranes arising from HIV-induced cell fusion, as well as syncytium formation between infected and non-infected cells and those involved in transduction, viral DNA nuclear import and virion budding from the host cell, are all made of proteins, a phospholipid (P) bilayer and cholesterol (C). However, the P/C molar ratio is higher in the retroviral envelope than in the plasma membrane where they originate, and higher than in the nuclear envelope. Mechanisms are described which elucidate this puzzling fact, as well as cholesterol-dependent leakage and pore formation during cell fusion. Fatty acylation of viral and host cell proteins is required to direct them to membranes. Detergent-insoluble microdomains enriched in cholesterol and sphingolipids, termed either DIGs (detergent-insoluble glycolipid-enriched complexes), DRMs (detergent resistant membranes), TIFFs (Triton-insoluble floating fractions) or GEMs (glycolipid-enriched membranes), function as platforms for attachment of proteins in the process of signal transduction. HIV-SUgp120 (HIV-surface glycoprotein), T-cell receptor (TCR)-CD4+ and co-receptors promote aggregation of these lipid "rafts" which concentrate the Src family tyrosine kinases SFKs (PTK, Lyn, Fyn, Lck), GPI (glycosyl phosphatidylinositol)-anchored proteins, and phosphatidylinositol kinases PI(3)K and PI(4)K, inducing cell signalling. HIV-SUgp120 transduces the activation signal and provokes the formation of polyunsaturated fatty acid (PUFA) metabolites, i.e. the prostaglandin PGE2 suppressor of immune function and inhibitor of cytotoxic T-lymphocyte (CTL) proliferation, while PGB2 activates SFKs and increases mRNA expression, as well as NFkappaB (nuclear transcription factor) translocation to nucleus. HIV nuclear import, DNA integration, chromatin template capacity may be mediated by the lipid environment. The lipid-enriched microdomains from which HIV-1 buds, may explain the high level of cholesterol and sphingolipids in the viral envelope, since host cell rafts become a viral coat. HIV-1 infection induces alteration of cellular lipids (1) shift in phospholipid synthesis to neutral lipids associated with the viral

load, polyunsaturated fatty acid (PUFA) peroxidation, and n-3 deficiency with deregulation of cytokines and PPAR-gamma (peroxisome proliferator-activated receptor-gamma), and (2) alloimmune phospholipid antibody production in which antibodies to cardiolipin and to phosphatidylserine are most prevalent, due to the destruction of mitochondrial membranes and progression of lymphocyte apoptosis. The current highly active anti-retroviral therapy, including both viral reverse transcriptase (RT) inhibitors (NRTIs and NNRTIs, nucleoside and non-nucleoside RT inhibitors) and protease inhibitors (PIs), induces side-effects in the long term. Lipodystrophy (LD), consists of peripheral lipoatrophy associated with central fat accumulation (called "crixibelly" and "buffalo hump"), insulin resistance, elevation of very low density lipoproteins, decrease in high density lipoproteins and inhibition of adipocyte differentiation. LD syndrome appears to be induced by PIs that inhibit GLUT4, glucose transporter isoform, and by NRTIs which provoke mitochondrial failure. New therapeutic strategies assessed: (1) inhibition of viral integrase and/or HIV entry into cells through natural products or their derivatives, (2) inhibition of HIV-1 entry into macrophages pretreated with Gram-negative bacterial lipopolysaccharide, (3) vaccination with multi-lipopeptides, i.e. sequences of HIV-1 peptides with CD4+ T-cell and B-cell epitopes, modified by adding a lipid tail to one end, which produce HIV-specific CTL and multispecific immune responses in most of the vaccinated subjects and (4) stimulation of antiviral drug activity with lipid-prodrugs targeting viral RT, polymerase, integrase, or aspartyl-protease.

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